Improving the odds:

reducing perinatal HIV transmission

Report of the Recommendations of
the Maternal Child Health Advisory Committee

Subcommittee on Perinatal HIV Reduction

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Michigan Department of Community Health

MDCH

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INTRODUCTION

Caring for women with human immunodeficiency virus (HIV) or who are at risk for HIV is a challenging task for health care providers in today's environment. Improving the Odds offers providers current information on the reduction of perinatal HIV transmission based on the results of the clinical trial ACTG 076 and more recent information about the medical therapy of people with HIV. It also offers information on effective approaches for offering HIV counseling and testing to women. Much of this information is adapted from the U.S. Public Health Services' Program Advisory: Use of Zidovudine to Reduce Perinatal HIV Transmission in HRSA-Funded Programs (HRSA, 1996) and the U.S. Public Health Service Recommendations for Human Immunodeficiency Virus Counseling and Testing for Pregnant Women (Centers for Disease Control and Prevention [CDC], 1995c), which was amended for use in Michigan by the Maternal Child Health Advisory Committee's Subcommittee on Perinatal HIV Reduction.

During the past decade, HIV infection has become one of the leading causes of morbidity among women. Women have accounted for one of the most rapid increases in cases of Acquired Immunodeficiency Syndrome (AIDS) in recent years. As the incidence of HIV infection has increased among women of childbearing age, increasing numbers of children have become infected through perinatal (i.e., mother to infant transmission). Almost all children with HIV infection acquire the virus by transmission from their mother. The risk of such transmission in the absence of intervention is 15 to 30%, with estimates ranging from 13-45%. Infection is acquired in utero 20% of the time, and 80% of transmission occurs in the peripartum period. Breast feeding also increases the risk of transmission.

Between 8,500 and 11,500 people in Michigan are estimated to have HIV disease. Of these, 69% are estimated to live in the Detroit metropolitan area. Nearly all of Michigan's 83 counties have persons living with HIV. About 80% of HIV/AIDS cases in Michigan are men and 20% are women. However, cases among women have increased faster than cases among men, so that the gap between men and women is steadily narrowing. Women account for approximately 75% of all people who acquired HIV infection through heterosexual contact. Rates of HIV/AIDS are seven times greater among blacks than among whites. Additionally, cases among blacks are increasing faster than cases among whites. More than 75% of women with AIDS are black. Three quarters of the infected population are adults age 25-44. This age group is a major subset of the female population considered to be in their reproductive years.

Children and adolescents account for 3% of total reported HIV/AIDS cases. According to the survey of women of childbearing age, approximately 80 women gave birth to HIV perinatally-exposed children in 1993, while in 1994, approximately 60 women gave birth to such children. The trend seen in this survey may indicate that HIV is decreasing among women of childbearing age or that fewer HIV-positive women are giving birth. However, there are no firm data which indicate that HIV is decreasing among women who are not giving birth.

This guide presents general approaches to medical management of pregnant women and their infants. Because of the rapid development of new therapies for treatment of HIV infection, this guide is not intended to represent the specifics of therapy in women infected with HIV. Women's health care providers caring for a pregnant woman with symptomatic HIV disease should seek consultation from a clinician who has expertise in HIV disease and work closely with the woman herself when making management decisions.

EXECUTIVE SUMMARY

In the United States, the incidence of infection with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) has increased among women of childbearing age. For instance, in 1994, approximately 22% of the 68,171 cases of HIV infection reported among adults and adolescents were female and 1,159 (1.7%) cases were pediatric HIV infection. In February 1995, the Centers for Disease Control and Prevention (CDC) reported that women accounted for 18.1% of the 440,000 reported AIDS cases. This percentage is twice as high as the percentage of women among the first 100,000 reported cases of AIDS (9%). Projections for the year 2000 indicate that at the current pace, as many as 125,000 children and adolescents will have lost their mothers to HIV/AIDS in the United States.

As of January 1997, Michigan ranked 17th in total HIV/AIDS cases reported; ranked 36th by annual rate per 100,000 population in the United States; and reported a cumulative total of 88 perinatal HIV cases. Of the 88 infants born with HIV, 42 (53%) were female. Moreover, since 1990, the annual reported incidence of women and children (age 0-13) with AIDS has tripled, while approximately 2 in 7 of the infants born to HIV infected women each year are infected with the virus.

Studies on HIV/AIDS have shown that reductions in perinatal HIV transmission would significantly reduce the number of children with AIDS. The Michigan Department of Community Health (MDCH) Maternal and Child Health Advisory Committee convened the Subcommittee on Perinatal HIV Reduction in March 1996 to examine the CDC Guidelines aimed at reducing the perinatal transmission of HIV and tailor them to the specific needs of Michigan residents. A 60-member advisory committee was selected from a variety of organiza-

tions serving women, children and infants, and also included consumers. The primary focus of the Subcommittee centered on the "CDC Recommendations for Universal Counseling and Voluntary Testing for HIV of Pregnant Women" and the "Clinical Guidelines for the Use of Zidovudine Therapy in Pregnancy to Reduce Perinatal Transmission of HIV", as developed by the New York State Department of Health - AIDS Institute.

The CDC Recommendations for Universal Counseling and Voluntary Testing for HIV of Pregnant Women were written and issued for pregnant women in the United States with the goal of providing the best opportunity for pregnant women to be educated about HIV, its transmission, and to learn their infectious status. These recommendations call for routine HIV counseling and voluntary testing of all pregnant women. Women who are HIV infected can be offered interventions to reduce the risk of perinatal and other transmission and obtain needed follow-up care for themselves and their infants. The Subcommittee supports these recommendations and has modified them specifically for implementation in Michigan. The purpose of HIV testing is not to label a woman as infected, but rather to engage her and her child in appropriate health care. This is most likely to occur when a woman feels she has participated in decisions regarding her own and her child's health. The first portion of this document contains these guidelines adapted by the Subcommittee for use in Michigan.

The Clinical Guidelines for the Use of Zidovudine Therapy in Pregnancy to Reduce Perinatal Transmission of HIV section deals with the results of the National Institutes of Allergies and Infectious Diseases' (NIAID) AIDS Clinical Trial Group (ACTG) protocol No. 076. The study, sometimes referred to as ACTG 076, demonstrated a substantial reduction in the transmission of HIV from mothers who were HIV positive to their infants when mothers and their infants were treated with zidovudine (AZT/ZDV). The study indicated that mother to child HIV transmission decreased from 25.5% to 8.3% for those mother/infant pairs who received antepartum, intrapartum and newborn AZT/ZDV therapy. These guidelines, since revised, represent the current standard of care therapy to reduce perinatal transmission of HIV.

Maternal and child health providers serve more than 16 million women, infants, children and youth and provide prenatal care for

roughly one-third of all pregnant women in the United States. With the ability to reach so many women and infants with effective maternal and child health services, state maternal and child health programs serve a central role in developing and implementing policies and programs that support the delivery of preventive health services to women and infants–services that have the potential to not only result in reducing perinatal transmission of HIV infection, but also to promote earlier intervention and earlier referral to care. It is important to note that substance abuse treatment and prevention providers play an important role in serving women and children and must be included in the group of maternal and child health service providers, along with the many private providers that serve women, children, adolescents and families.

This reference document should be kept readily available in the office of all providers that serve women, children and adolescents. The summarized recommendations are provided for quick reference; however, the full version of this document is written in a manner that supports understanding and provides additional references.

Contact the Michigan Resource Center at 1-800-626-4636 for additional copies of this document.

RECOMMENDATIONS FOR UNIVERSAL COUNSELING AND VOLUNTARY TESTING OF PREGNANT WOMEN FOR HIV

HIV Prevention and Treatment Opportunities for Women and Infants

1. HIV counseling and testing for women of childbearing age offer important prevention opportunities for both uninfected and infected women and their infants. Such counseling is intended to:

   a. Assist women in assessing their current or future risk for HIV infection;

   b. Initiate or reinforce HIV risk reduction behavior; and

   c. Allow for referral to other HIV prevention services (e.g., treatment for substance abuse and sexually transmitted diseases) when appropriate.

2. For infected women, knowledge of their HIV infection status provides opportunities to:

   a. Obtain treatment for themselves and diagnosis and treatment for their infants;

   b. Make informed reproductive decisions;

   c. Use methods to reduce the risk for perinatal transmission;

   d. Receive information to prevent HIV transmission to others; and

   e. Obtain referral for psychological and social services, as needed.

3. Interventions designed to reduce morbidity in HIV infected persons require that HIV infection be diagnosed so that treatment can be initiated.

4. Providing HIV counseling and testing services in gynecologic,

prenatal and other obstetric settings presents an opportunity for early diagnosis of HIV infection because many women access the health care system for obstetric or gynecologic-related care.

HIV Counseling and Voluntary Testing of Women and Their Infants

1. Health care providers should ensure that all pregnant women are counseled and encouraged to be tested for HIV infection to allow women to know their infection status both for their own health and to reduce the risk for perinatal HIV transmission. Substance abuse screening and treatment services should also be provided. Pretest HIV counseling of pregnant women should include information regarding the risk for HIV infection associated with sexual activity and alcohol and other drug abuse, the risk for transmission to the woman's infant if she is infected, and the availability of therapy to reduce this risk. HIV counseling, including any written materials, should be linguistically, culturally, educationally, and age appropriate for individual patients.

2. Michigan law requires that:
   a. All pregnant women be counseled about, and tested for, HIV;
   b. HIV testing of pregnant women and their infants must be voluntary;
   c. Written, informed consent for testing be obtained prior to testing;
   d. Women who test positive for HIV or who refuse testing must not be:
      - denied prenatal or other health care services,
      - reported to child protective service agencies because of refusal to be tested or because of their HIV status, or
      - discriminated against in any other way, and
   e. Documentation of whether testing was accepted/refused and the date that it occurred must be in each client's chart.

3. All uninfected pregnant women should be encouraged to avoid exposure to HIV. Those uninfected pregnant women who continue to practice high risk behaviors (e.g., alcohol and other drug use, including crack cocaine, infection with a sexually transmitted disease,

such as chlamydia, and unprotected sexual contact with an HIV infected or high-risk partner) should be retested for HIV in the third trimester of pregnancy and referred to appropriate services, including drug treatment.

4. In order that HIV counseling and testing be readily available to all people, specific strategies and resources will be needed to communicate with women who may not obtain prenatal care because of homelessness, incarceration, undocumented citizenship status, drug or alcohol abuse, or other reasons. Health care providers should be aware of the complex issues that HIV infected women must consider about their reproductive options, and reproductive counseling should be non-directive.

5. The prevalence of HIV infection may be higher in women who have not received prenatal care. These women should be assessed promptly for HIV infection. Such an assessment should include information regarding prior HIV testing, test results, and risk history. For women who are first identified as being HIV infected during labor and delivery, health care providers should consider offering intrapartum and neonatal ZDV according to published recommendations. For women whose HIV infection status has not been determined, HIV counseling should be provided and HIV testing offered as soon as the mother's medical condition permits. **However, involuntary HIV testing must never be substituted for counseling and voluntary testing.** Both confidential and anonymous testing should be made available and supported as allowed by law.

6. Testing should be considered for babies, and in some instances, older children, of women who are HIV-positive or whose HIV status is unknown. Testing should be done in accordance within prevailing legal requirements, and with the consent of the legal guardian and of the biologic mother (if she is not the legal guardian), when possible. Counseling should include the risks for HIV, the benefits to knowing a child's infection status, the need for follow-up and early medical intervention in the event the child tests positive, and the understanding that a positive HIV test in a baby is indicative of infection in the mother. Foster care agencies must assure referral for early medical intervention and monitoring when indicated for HIV-positive children in their care.

7. Pregnant women, regardless of their infection status, should be provided access to other HIV prevention and treatment services (e.g., substance abuse treatment, partner-notification services, case management, mental health services, etc.) as needed. Referrals should be made at the time the women receive counseling and health care providers should ensure that appointments are made. Health care providers should make the follow-through process as easy as possible for women by providing clear instructions on where they are to go and make appointments to facilities which are accessible to the client. Effort should be made to make counseling and testing easily available, including use of mobile units, the use of community- based organizations and other appropriate agencies.

Interpretation of HIV Test Results

1. HIV antibody testing should be performed according to current recommendations, which includes the use of an enzyme immunoassay (EIA) to test for antibody to HIV and confirmatory testing with an additional, more specific assay (e.g., Western blot or immunofluorescence assay [IFA]). All assays should be performed and conducted according to manufacturers' instructions and applicable state and federal laboratory guidelines.

2. All patients to be tested for HIV antibodies should be provided with pre- and post-test counseling in compliance with Michigan State HIV Mandatory Counseling and Informed Consent Law (Act 488 of 1988, as amended by Act 200 of 1994, and Act 420 of 1994-Section 5133).

   HIV positive test results shall be reported to a local health department within seven days on a form provided by the Michigan Department of Community Health (CDC 50.42A or CDC 50.42B in compliance with HIV Reporting Law (Act 489 of 1988-Section 5114).

3. HIV testing of all women of childbearing age must be voluntary. Written informed consent for testing must be obtained as required by Michigan law. Women who test positive for HIV or who refuse testing should:

a) not be denied prenatal or other health care service,

b) receive assurance that they will not be reported to child protective service agencies, nor lose custody of their children, because of refusal to be tested or because of their HIV status,

c) not be discriminated against in any other way.

4. HIV infection (as indicated by the presence of antibody to HIV) is defined by Michigan law as a repeatedly reactive EIA and a positive confirmatory supplemental test. Women with persistent indeterminate test results should be referred for further definitive antigen based testing (e.g., PCR). Pregnant women who have repeatedly reactive EIA and indeterminate supplemental tests should be retested immediately for HIV antibody to distinguish between recent seroconversion and a negative test result. Women with a positive test should always be retested to confirm the positive status. Uncertainties regarding HIV infection status should be resolved before final decisions are made concerning pregnancy termination, ZDV therapy, or other interventions.

5. Women who have negative EIAs and those who have repeatedly reactive EIAs, but negative confirmatory tests, should be considered uninfected.

6. Pregnant women with negative tests should receive a full explanation of what a negative test means and include that explanation in the context of the client's risk.

Recommendations for HIV Infected Pregnant Women

1. HIV infected pregnant women should receive counseling as previously recommended in the CDC, 1994 document "HIV Counseling, Testing and Referral: Standards & Guidelines from the U.S. Department of Health & Human Services". Post test HIV counseling should include an explanation of the clinical implications of a positive HIV antibody test result and the need for, benefit of, and means to access HIV related medical and other early intervention services. Such counseling should also include a discussion of the interaction between pregnancy and HIV infection, the risk for perinatal HIV transmission and ways to reduce this risk, the

prognosis for infants who become infected, and available existing support services and reasonable linkages with those services.

2. HIV infected pregnant women should be evaluated according to published recommendations to assess their need for antiretroviral therapy, antimicrobial prophylaxis, and treatment of other conditions. Although medical management of HIV infection is essentially the same for pregnant and non-pregnant women, recommendations for treating a patient who has tuberculosis have been modified for pregnant women because of potential teratogenic effects of specific medications (e.g., streptomycin and pyrazinamide). HIV infected pregnant women should be evaluated to determine their need for psychological and social services, and referrals made as appropriate. All providers including managed care providers should ensure that support services are available to women.

3. HIV infected pregnant women should be provided information concerning ZDV and current accepted drug therapy to reduce the risk for perinatal HIV transmission. This information should address the potential benefit and short-term safety of ZDV and the uncertainties regarding:

   a. long-term risks of such therapy, and

   b. effectiveness in women who have different clinical characteristics (e.g., CD4+ T-lymphocyte count and previous ZDV use) than women who participated in the trial.

   HIV infected pregnant women should be encouraged, but not coerced, into taking ZDV therapy. Decisions should be made after consideration of both the benefits and potential risks of the regimen to the woman and her child. Therapy should be offered according to the appropriate regimen in published recommendations. A woman's decision not to accept treatment should not result in punitive action or denial of care.

4. HIV infected pregnant women should receive information about all reproductive options. Health care providers should be aware of the complex issues that HIV infected women must consider when making decisions about their reproductive options, and reproductive counseling should be non-directive.

5. To reduce the risk for HIV transmission to their infants, HIV infected women should be advised against breast feeding. Support services should be provided when necessary for use of appropriate breast-milk substitutes (including available supplemental food programs).

6. Confidential HIV related information should be disclosed or shared only in accordance with Michigan law. To optimize medical management and comply with current law, counseling and testing acceptance or refusal should be documented. Positive or negative HIV test results should be available to a woman's health care provider and included on both her and her infant's confidential medical records. Providers should obtain from the mother a written release of information, specific for HIV-related information, which includes to whom, for what purposes, and for how long information will be released. After consulting with the mother, maternal health care providers should notify the pediatric care providers of the impending birth of an HIV exposed child, any anticipated complications, and whether ZDV should be administered after birth. If HIV is first diagnosed in the child, the child's health care providers should discuss the implication of the child's diagnosis for the woman's health and assist the mother in obtaining care for herself.

7. Counseling for HIV infected pregnant women should include an assessment of the potential for negative effects resulting from HIV infection (e.g., discrimination, domestic violence, and psychological difficulties). For women who anticipate or experience such effects, counseling also should include:

   a) information on how to minimize these potential consequences,

   b) assistance in identifying supportive persons within their own social network, and

   c) referral to appropriate psychological, social, and legal services.

   In addition, HIV infected women should be informed that discrimination against persons who are HIV infected, in matters

such as housing, employment, state programs, and public accommodations (including physicians' offices and hospitals) is illegal.

8. HIV infected women should be encouraged to allow HIV testing of any of their children born after they became infected or after 1977 if they do not know when they became infected. Testing of older children should be done with the child's informed consent or assent. Women should be informed that the lack of signs and symptoms suggestive of HIV infection in older children does not necessarily indicate a lack of HIV infection; some perinatally infected children can remain asymptomatic for many years.

Recommendations for Follow-Up of Infected Women and Perinatally Exposed Infants

1. Following pregnancy, HIV infected women should be provided ongoing HIV related medical care, including immunological monitoring, antiretroviral therapy, and prophylaxis for and treatment of opportunistic infections and other HIV related conditions. HIV-infected women should receive gynecologic care, including regular Pap smears, reproductive counseling, information on how to prevent sexual transmission of HIV and other STD's and treatment of gynecologic conditions according to published recommendations.

2. HIV infected women who are substance abusers should be assessed for substance abuse treatment readiness and referred appropriately.

3. HIV infected women (or the guardians of their children) should be informed of the importance of follow-up for their children. These children should receive follow-up care to determine their infection status, to initiate prophylactic therapy to prevent PCP according to most recent recommendations, to determine the need for antiretroviral and other prophylactic therapy and to initiate regular pediatric care. HIV infected children and other children living in households with HIV infected persons should be vaccinated according to published Recommendations of the *Advisory Committee on Immunization Practices* (ACIP).

4. In situations where a mother is known to be HIV positive and does not have custody of one or more of her biological children, there should be legal provisions (mechanisms) to notify the children's guardian of the need for HIV testing and care.

5. In situations where a child is known to be HIV positive and no longer resides with their biological mother (i.e., as in foster care), there should be legal provisions (mechanisms) to notify the child's biological mother of the need for HIV testing and care.

CONSUMER/COMMUNITY RECOMMENDATIONS

Services for women infected and affected by HIV must meet the needs of the clients served. In order for that to be accomplished, comments and concerns from those individuals receiving services must be considered in system development. The following recommendations were provided by the Consumer and Community-Based Organizations Workgroup of the Subcommittee on Perinatal HIV Reduction. The members of this workgroup included women infected and affected by HIV and representatives of community-based organizations involved in HIV/AIDS related service delivery. During the discussion two concerns were expressed:

1. Not all Family Planning Clinics have routine HIV counseling and testing services, and

2. Physicians who do not have HIV counseling and testing services do not refer clients elsewhere.

The consensus of the committee was that the PHS recommendations are very broad and sounded good on paper but need to specifically relate to implementation in Michigan. The following recommendations provide an implementation strategy.

Recommendations:

1. **Physicians, nurses, social workers, clerical staff, and other health care workers who will come in contact with clients need education and training in client-centered counseling.**

   Many women do not know how to express their needs. Therefore, health care workers serving this population must be able to facilitate the conversation and ask appropriate questions to assist women in verbalizing their needs. This is especially necessary in high risk situations.

2. **Counseling must be done in a way which does not compromise women's sexual relationships, especially in instances when they are in one-partner sexual relationships.**

   Many women may not perceive themselves as being at risk because they are in monogamous relationships.

3. **Recruit women who are HIV positive and/or from high at-risk populations to serve as advocates. The women who are recruited as advocates need to go through a training program.**

   There is a need for more advocates. Advocates should come from women who are HIV positive and/or high at-risk populations and need to receive training in their advocacy role. They need skills in communication, knowledge about community resources, etc.

4. **The state needs to provide financial resources to support outreach efforts. Women who are HIV positive and/or are from high at-risk populations should be recruited to do the outreach. Women who are recruited as outreach workers need to be provided incentives and receive monetary compensation.**

   There should be a strong and expanded outreach component as part of any Perinatal HIV Reduction Program. Few women from

the African-American community can stand up and acknowledge they are positive.

5. **All appropriate referrals must be made at the time the women receive counseling. Health care providers must ensure that appointments are made. Health care providers must make the following through process as easy as possible for women by providing clear instructions on where they are to go, make appointments to facilities which are accessible to the client, etc. Every effort must be made to accommodate the needs and preferences of the client. Mobile units should be used for testing. They can be taken to community-based organizations and other appropriate agencies.**

   Referrals must be made at the time women are seen. The health care provider must take the initiative to make the referral, set-up appointments, if needed, and ensure that the women get to their appointments. Referrals must be made according to the clients preference, taking into account the accessibility of service. Every effort must be made to accommodate the needs of the women.

6. **Providers should obtain at least two telephone numbers from clients to assist with follow-up.**

   Follow-up for women identified as HIV positive is important. Also, it is important to develop trust and a bond between client and provider.

7. **Establish ways of getting information out to the community and providers about the support groups and other programs available to HIV positive women and women at risk.**

   Women should be provided support groups. There are five or six programs that work with women who are HIV positive in the Detroit area, however, many women do not know about these programs. There is a lack of information and awareness in the community.

8. **Use community-based organizations who have experience serving specific populations and where women feel comfortable. Community-based organizations staff need**

to be educated and trained on subjects like HIV counseling and testing, substance abuse, etc. Referrals and resources must be readily available for women who test positive, as well as those who do not test positive, and also for those whose specific needs have been identified.

There should be a family focus, recognizing that the whole family is affected not just the woman who is HIV positive. Health care providers, counselors, and agencies must have the capacity to make appropriate and timely referrals and do follow-up for the entire family.

9. **State recommendations must include language that protects women from being reported to protective service agencies because of refusal to be tested or because of their HIV status. The recommendations should also assure that women will not lose custody of their child(ren) because of their refusal to be tested or because of their HIV status.**

   Most women are good mothers and are very concerned that their children will be taken away if they test positive.

10. **Develop support groups for HIV positive women.**

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LINICAL GUIDELINES

FOR THE USE OF

ZIDOVUDINE THERAPY IN

PREGNANCY TO REDUCE PERINATAL

TRANSMISSION OF HIV

Special acknowledgement and recognition is extended to the AIDS Institute of New York and Theodore Jones, M.D., Hutzel Hospital, Detroit for the development of this section.

INTRODUCTION

Women now constitute one of the fastest-growing populations of those infected with HIV. Currently, women account for 15% of the cumulative cases of acquired immunodeficiency syndrome (AIDS) reported in Michigan and the United States. In 1996, 20% of the new cases of AIDS among adults and adolescents reported to the CDC were women. The vast majority of these HIV-positive women are of reproductive age. Estimates in recent years indicate approximately 7,000 HIV infected women have given birth annually in the United States. When one assumes a 15-30% perinatal transmission rate, an estimated 1,000-2,000 HIV infected children are born each year in the United States. These children with perinatally acquired HIV infection account for over 90% of the pediatrics AIDS cases in the United States.

The transmission of HIV from mother to infant may occur during pregnancy, labor, and delivery as well as postpartum via breast feeding. When considering the most likely time of transmission, the period at or around delivery may contribute 65 to 70% of infected babies. In contrast, a smaller percentage of infants are infected in utero or through breast feeding.

In February, 1994 the National Institutes of Health in collaboration with the National Institute of Health and Medical Research in the National Agency of Research of AIDS in France announced the results of a randomized trial, AIDS Clinical Trial Group (ACTG) protocol 076, that demonstrated that a regimen of zidovudine (ZDV) given to a selected group of HIV infected pregnant women and their newborns reduced the risk of perinatal transmission by two-thirds. This dramatic finding holds the potential for a significant decrease in HIV infection among children.

It is extremely important that all clinicians who care for pregnant women and their newborns, including primary care practitioners, obstetricians, pediatricians, family medicine practitioners, HIV specialists, midwives, registered nurses, and physician assistants, are well informed about the data from the ACTG 076 trial and its clinical implications. A comprehensive understanding of ZDV treatment for

pregnant women with HIV infection and for their infants will help the provider to best guide patients to make decisions that will reduce, to the extent possible, the risk of vertical transmission of HIV.

ACTG 076 Trial Summary

The National Institutes of Health initiated a clinical trial in 1991 called the AIDS Clinical Trial Group 076 (ACTG 076) to determine whether zidovudine (ZDV) could reduce perinatal transmission of HIV. The women enrolled in this study had the following characteristics:

- HIV infection
- Pregnancy for at least 14 weeks gestation and no greater than 34 weeks gestation;
- No antiretroviral therapy during the current pregnancy;
- No indications for maternal ZDV therapy, i.e., CD4+ cell count $\geq$ 200.

The study randomly assigned women to receive either ZDV or a placebo. The study medication was taken orally during the antepartum period, was given intravenously during labor, and was given to newborns orally for the first six weeks of their life within 24 hours of birth. Dosages used for the ACTG 076 protocol were as follows:

Antepartum	Oral administration of 100 mg ZDV five times daily, initiated at 14-34 weeks gestation and continued throughout the pregnancy.
Intrapartum	During labor, intravenous administration of ZDV in a 1-hour loading dose of 2 mg per kg of body weight, followed by a continuous infusion of 1 mg per kg of body weight per hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg body weight per dose every 6 hours) for the first six weeks of life, beginning at 8-12 hours after birth. (Note: intravenous dosage for infants who cannot tolerate oral intake is 1.5 mg per kg body weight intravenously every six hours).

In total, 477 women and their infants (421 babies were born during the study period) were enrolled as of December 1993. The participants' racial and ethnic backgrounds were reflective of women with HIV infection in the United States: 79% were either African-American or Hispanic.

On February 21, 1994, results of an interim evaluation of the study were announced. Preliminary findings involving 363 infants showed that HIV transmission was reduced by two-thirds, from 25.5% in infants whose mothers were assigned to placebo to 8.3% in infants receiving ZDV. The beneficial treatment effect of ZDV was seen in all subgroups analyzed, regardless of maternal CD4+ cell count, maternal drug use, maternal co-infections, or type of delivery.

ZDV was well tolerated by mothers and infants. The only observed short-term infant toxicity was a decrease in mean hemoglobin of approximately 1 g/dL. The maximum difference in mean hemoglobin levels between the two groups occurred at 3 weeks of age, and the lowest absolute hemoglobin was reported at 6 weeks of age. Anemia resolved by 12 weeks of age in newborns. No infant required transfusions, although some infants required ZDV dose reduction or dose interruption.

There were three limitations in the study which deserve mention. The design of the study did not permit the determination of the most beneficial time of treatment: before, during, or after delivery. The long-term safety of the ACTG 076 trial regimen remains unknown (but will be assessed by longitudinal follow-up of both the mothers and the children who participated in the trial). Finally, women with advanced HIV disease were not studied and, therefore, the study gives no information about outcomes in these women.

After delivery, women were followed for six months. Once the benefit of ZDV was revealed, open label medication was offered to all women. A follow-up study to monitor the effects of study participation upon women's health for 3 years after delivery was begun. Infants were followed until 18 months to confirm their HIV status. When all infants had reached the age of 18 months (January 1996), the study

was ended. The infants are all eligible to participate in a follow-up study (until age 21) to identify any long-term effects of ZDV.

Identification of Pregnant Women with HIV Infection and Documentation of Maternal HIV Antibody Status

All obstetricians, midwives, family practitioners, and other obstetrical care providers should routinely discuss the risk of perinatal HIV transmission with their patients. All health care providers who work with women should routinely offer and recommend HIV antibody testing for all pregnant women and all women considering pregnancy. Testing should be performed as early as possible during pregnancy. Women with on-going high risk behavior during pregnancy should be offered re-testing if negative on initial screening.

During admission for labor and delivery, routine history taking should include determination of HIV serostatus. Their assessment for HIV infection should include information regarding prior HIV testing, test results, and risk history. The Prenatal Care Requirement of the Michigan Law (Act 491 of 1988, as amended by Act 200 of 1994-Section 5123) requires that:

Pregnant women be offered counseling and be tested for HIV, hepatitis B, and venereal disease at the time of the woman's first prenatal visit unless the tests are medically inadvisable, or the woman refuses consent to be tested. Moreover, if the woman has not been previously tested, and she presents at a health care facility for delivery, or for care in the immediate postpartum period following delivery outside of a health care facility, the law also states that the woman should be tested unless medically inadvisable, or if she refuses consent.

If the institution at which a woman delivers cannot document her HIV serostatus or that she declined testing, it will be necessary for these women to receive HIV counseling and be offered testing as soon as the mother's medical condition permits. This is especially important in women who have received no prenatal care, since the prevalence of HIV infection may be higher in these women. For those women who are known to be HIV infected, a history of antepartum ZDV use

should also be obtained in order to facilitate intrapartum treatment. In situations where medical documentation of maternal infection is not available and the woman states that she is HIV infected, therapy may be offered and initiated while awaiting serological confirmation.

Occasionally, women will decline to choose testing after HIV counseling has been provided. In such cases, it is important to ensure: 1) enough information about HIV and the test has been provided; 2) that it was provided in an understandable, believable, and supportive way; and 3) that no confusion has resulted about her options and the risks and benefits of ZDV therapy. This information should be communicated as routine obstetrical care to help patients make an informed decision about HIV testing.

Guidelines for the Administration of ZDV for the Prevention of Mother to Child HIV Transmission

Important Clinical Considerations

Clinical guidelines are dynamic and change frequently as new scientific insights allow clinicians to use different and frequently improved interventions to battle and control HIV infection. HIV infected pregnant woman should be evaluated according to published recommendations to assess their need for antiviral therapy, antimicrobial prophylaxis, and treatment of other conditions. New understandings concerning the biology of HIV center around the viral dynamics of the infection. The discovery that there is a much greater and more rapid rate of viral turnover during all stages of HIV-1 infection than was previously recognized has radically changed the way we think about the treatment and care of HIV infection. Therapeutic interventions now focus on the initiation of early aggressive combination antiretroviral regimens to maximally suppress viral replication while sustaining immune function and reducing the development of resistance.

The combination of two laboratory results, the absolute (or percent) CD4+ lymphocyte count, and the quantitative measure of plasma HIV

RNA (often called the viral load) provide much more prognostic information than either alone. A patient's level of plasma HIV RNA strongly indicates the expected rate of progression of their HIV disease. Higher RNA levels correlate with more rapid progression. Quantitative plasma HIV RNA can be measured using one of three tests (RT-PCR known as Amplicor by Roche, bDNA by Chiron, and NASBA by Organin Technika), but results should not be compared across methods. Further, because of variability in all of these tests, baseline values before treatment are best obtained by averaging two separate assays on two separate specimens drawn on different days. Since acute illnesses and vaccinations can transiently raise viral load, HIV RNA testing should be postponed several weeks following an illness or vaccination. A patient's CD4+ lymphocyte count indicates how far immune destruction has progressed. A patient with a low viral load (<3000 copies by RT-PCR) and high CD4+ count (>750 cells) has nearly zero probability of progressing to AIDS within 3 years, whereas a patient with a high viral load (>10,000 copies by RT-PCR) and low CD4+ count (<200 cells) has an 86% chance of developing AIDS within the next 3 years.

Current recommendations strongly encourage combination antiretroviral therapy for all persons who have acquired their HIV infection (not merely had their first positive test) within the past three to six months, all persons who have either a CD4+ lymphocyte count less than 350-500 cells or a plasma HIV RNA greater than or equal to 10,000 copies/ml, and all persons with symptomatic HIV disease. Antiretroviral treatment is considered optional for those asymptomatic HIV-infected persons with both CD4+ lymphocyte counts greater than 350-500 cells/mm^3, and plasma HIV RNA levels less than 10,000 copies/ml.

HIV-infected pregnant women should be evaluated according to published recommendations to assess their need for antiviral therapy, antimicrobial prophylaxis, and treatment of other conditions. Although medical management of HIV infection is essentially the same for pregnant and non-pregnant women, recommendations for treating a pregnant patient must consider issues of potential embryo toxicity and fetal toxicity. HIV-infected pregnant women should be evaluated to determine their need for psychological and social services.

In the ACTG 076 trial, zidovudine monotherapy was intended to decrease mother to child transmission of HIV and was not prescribed

to stabilize the health of women with HIV infection. With the demonstration of the superiority of combination therapy when compared to antiretroviral monotherapy, ZDV therapy alone is now considered suboptimal for the treatment of HIV infection. ZDV monotherapy should only be considered for pregnant women for whom combination antiretroviral therapy is not recommended or is refused. Throughout pregnancy, clinicians should evaluate women with HIV infection for clinical and immunologic disease progression and for the need for antiretroviral therapy for maternal indications. In women with advanced immunosuppression, antiretroviral therapy for maternal indications should be recommended after consultation with a physician skilled in AIDS medicine.

Current treatment recommendations for HIV-1-infected pregnant women are based on the belief that therapies of accepted benefit to women should not be withheld during pregnancy unless there are documented adverse effects on the mother, fetus, or infant and these adverse effects outweigh the benefit to the woman. Since there is no compelling evidence of additional risk or data to support a therapeutic advantage to the use of an alternative therapy, the guidelines for optimal antiretroviral therapy in pregnant HIV-1 infected women should be the same as those delineated for non-pregnant adults. These complex regimens should be initiated and managed in consultation with clinicians experienced in HIV/AIDS care. Care givers should not forget that the potential impact of optimal therapy on the fetus and infant is unknown. Long-term follow-up is needed for children who have exposure to antiretroviral drugs *in utero*. Therefore, any decision to use any antiretroviral drug during pregnancy should be made by the woman following discussion with her health care provider regarding the known and unknown benefits and risks to her and her fetus.

In general, optimal combination antiretroviral therapy consists of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor and is the currently recommended standard treatment for non-pregnant HIV-1-infected adults with CD4 lymphocyte count $<500/mm^3$, HIV-1 RNA copy number >10,000/mL, or clinical symptoms

of HIV disease. A woman's pregnancy should not preclude the use of optimal therapeutic regimens though some qualification may exist.

Factors That May Influence Mother to Child Transmission

Multiple viral, immunological, and physical factors may influence the transmission of HIV from a pregnant woman to her infant. Some studies indicated that both increased maternal viral burden and advanced maternal immunosuppression have been associated with an increased risk of mother to child HIV transmission. Other important factors may include duration of membrane rupture (greater than four hours), delivery of a previously infected child, and potentially risky obstetrical interventions (placement of scalp electrodes, fetal scalp pH sampling, amniocentesis and percutaneous umbilical blood sampling).

Preliminary data suggest that pre-existing zidovudine resistance among previously treated women is associated with reduced efficacy of the ACTG 076 regimen. Therefore, women who have received prior zidovudine therapy should be considered for combination antiretroviral treatment. Some women may acquire zidovudine resistance without prior treatment. The effect of ZDV monotherapy on perinatal transmission in this circumstance is not known.

No data are available regarding safety and efficacy of other antiretrovirals during the intrapartum period and for initial treatment of exposed newborns. Therefore, intrapartum intravenous ZDV and newborn oral ZDV should be discussed and offered regardless of the mother's antiretroviral regimen. If possible, the mother's combination oral regimen should be continued during the intrapartum period with concurrent intravenous ZDV.

In cases where maternal HIV resistance to ZDV is suspected, it is unclear whether ZDV treatment will still reduce the risk of mother to child HIV transmission. Patients who are infected with ZDV-resistant viral strains are also likely to be infected with ZDV-sensitive strains. It is unknown whether ZDV-resistant strains are more likely or less likely to be transmitted. Consultation with an HIV specialist is important to ensure appropriate and adequate therapy.

The explanation for the success of the ZDV treatment regimen requires further scientific analysis. The mechanism by which ZDV reduced transmission in ACTG 076 is not fully defined. It is clear that the effect of ZDV on maternal HIV-1 RNA did not fully account for the observed efficacy of ZDV in reducing transmission. A growing consideration is that pre-exposure prophylaxis of the fetus-infant is an important component of protection. Therapeutic intracellular levels of ZDV in the fetus that were maintained through early infancy may have provided prophylaxis to the fetus-newborn prior to and immediately after exposure.

Side Effects of ZDV Therapy in the ACTG 076 Trial

In the ACTG 076 trial, maternal ZDV therapy was well tolerated. In general, the side effects commonly observed with ZDV therapy in adult patients have included headache and gastrointestinal intolerance. The other more serious adverse experiences reported among ZDV users, such as anemia, hepatitis, and steatosis/lactic acidosis, were not seen. The long-term effects on maternal health following a short course of antepartum ZDV are unknown. With increasing duration of ZDV therapy, there is the potential for diminished ZDV antiviral efficacy and/or the potential for the emergence of ZDV-resistant viral strains. The occurrence of these problems following only a short course of maternal ZDV therapy and the potential long-term impact on maternal health remain unknown.

Fetal/newborn therapy was also well tolerated in the ACTG 076 study. The only side effect observed was mild anemia. Long-term risks are unknown and may include unanticipated serious toxicities. The ACTG 076 study cohort of ZDV-exposed infants will be followed to assess whether ZDV may affect neurodevelopment, other organ function, or the risk for neoplasia.

Information concerning the safety of drugs in pregnancy comes from many sources, including animal toxicity data, anecdotal experience, registry data and clinical trials. Currently, there is little data available about the pharmacokinetics and safety of antiretrovirals during pregnancy for antiretrovirals other than ZDV. Without such information, choices of drugs should be individualized in discussions with the woman about data collected from preclinical and clinical testing of the individual drugs.

Patient Selection

The ACTG 076 study results should be reviewed and a discussion between the clinician and patient should occur. The clinician should recognize the concerns of the patient, weighing her desire to deliver a healthy, uninfected baby with her concerns about her own health and the status of her HIV infection. All discussions about ZDV therapy to reduce the risk of mother to child HIV transmission should include a full discussion of risks and benefits with the aim of educating women to make an informed decision about treatment. The clinician should conduct discussions with the patient in a manner that is culturally sensitive and linguistically and educationally appropriate to the patient.

Guidelines for Antiretroviral Therapy for the Interruption of Mother to Child HIV Transmission in Pregnant Women with HIV Infection

- **Women with CD4 cell counts > 500 and a viral load <10,000 copies with no prior ZDV treatment and who are >14 weeks gestation**

  RECOMMENDATION: Combined antepartum, intrapartum, and newborn ZDV regimen is recommended as per the ACTG 076 protocol.

- **Women with CD4 cell counts <500 and /or a viral load >10,000 copies and/or women with prior ZDV treatment who are >14 weeks gestation**

  RECOMMENDATION: Consultation with an experienced HIV clinician about the use of combination therapy. ZDV should be considered as part of the mother's antiretroviral regimen. Intrapartum and newborn ZDV should be discussed and offered regardless of the mother's combination regimen.

Whether therapy is initiated for the prevention of mother to child HIV transmission or for maternal medical indications, therapy should begin after 14 weeks gestation (after organogenesis is complete) due to the lack of first-trimester safety information. Intrapartum therapy

should be administered followed by six weeks of newborn ZDV therapy.

ZDV therapy may be beneficial for this population. If the decision is made to initiate ZDV therapy, antepartum therapy should begin as soon as possible, followed by intrapartum and newborn therapy.

- **Women in labor who have never received any antepartum maternal ZDV therapy (regardless of maternal CD4 cell count or viral load) and present in labor**

RECOMMENDATION: A ZDV regimen combining intrapartum and newborn therapy should be discussed and offered.

Since substantial transmission of HIV may occur at the time of labor and delivery, combined intrapartum/newborn ZDV therapy may provide some efficacy in reducing the risk of perinatal transmission. When indicated, intrapartum and neonatal therapy should be initiated without delay as outlined in these guidelines. When possible, combined intrapartum/newborn therapy is preferred to newborn therapy alone. It is strongly believed that early initiation of newborn therapy is likely to be more effective than delayed newborn therapy. Although no consensus was reached regarding an outside limit for the initiation of newborn ZDV therapy, it is unlikely that any benefit will be gained if therapy is started after 48 hours of life.

- **Women who are intolerant of ZDV**

RECOMMENDATION: Pregnant women who become intolerant of ZDV following initiation of therapy as per the ACTG 076 trial regimen should have their maternal therapy altered. A ZDV regimen combining intrapartum and newborn therapy should be discussed and offered.

The clinician should review the patient's history of ZDV intolerance.

A woman receiving antepartum therapy may be unable to tolerate ZDV either because of gastrointestinal intolerance, hematologic or hepatic toxicities, or other serious side effects. Depending on the nature of the toxicity, maternal therapy may need to be reduced, interrupted, or discontinued. If ZDV has been discontinued because of anemia or gastrointestinal intolerance, a single intrapartum infusion of ZDV would not be contraindicated. If ZDV has been discontinued because of severe or life-threatening toxicity, such as anaphylaxis, intrapartum therapy would be contraindicated. If maternal therapy is not given, newborn therapy may still be given.

Important Elements to Include in a Risk/Benefit Discussion of Antiretroviral Therapy to Prevent Mother to Child HIV Transmission

Maternal Considerations

1. Known risks and side effects for antiretroviral agents should be discussed. Possible side effects of ZDV include headaches and gastrointestinal intolerance, as well as reported toxicities, such as anemia, hepatitis, and steatosis or lactic acidosis. Appropriate clinical and laboratory monitoring is indicated.

2. Long-term side effects following short-term maternal ZDV therapy are unknown. Factors to consider include the unknown effect on maternal disease progression following a short course of ZDV therapy (or multiple short courses for multiple pregnancies), as well as the unknown effect of intermittent therapy on the development of ZDV drug resistance.

Fetal/Newborn Considerations

1. A combined antepartum, intrapartum, and newborn ZDV regimen has been shown to reduce the risk of mother to child HIV transmission by 67%.

2. Long-term neonatal or infant side effects following ZDV therapy are unknown. To date, no significant pattern of toxicities has been noted. The potential, however, for serious unanticipated toxicities cannot be dismissed.

3. The efficacy of combined intrapartum/newborn therapy without maternal antepartum therapy is unknown and has not been studied. Because intrapartum HIV transmission may occur, this therapeutic approach may have some efficacy in reducing mother to child HIV transmission.

4. When appropriate, important clinical issues to discuss about ZDV therapy include the lack of first-trimester safety information, the waning efficacy of ZDV's antiviral effect over time, and the increasing risk of ZDV resistance with prolonged therapy (especially if ZDV therapy has been accompanied by HIV related disease progression).

5. If other antiretroviral agents are prescribed for maternal indications, counseling should reflect that the impact on mother to child HIV transmission and on safety in pregnancy is unknown.

6. The only significant infant short-term side effect in the ACTG 076 study population was newborn anemia. Although other toxicities were not noted, potential problems include drug-induced hepatitis, as well as other possible unknown toxicities. Appropriate clinical and laboratory monitoring is indicated.

Recommendations for Monitoring of Antiretroviral Therapy

Maternal Therapy

Clinicians monitoring maternal ZDV therapy should order baseline and monthly complete blood count and liver function tests. Dose interruption or dose modification should be considered for a hemoglobin < 8.5 g/dL and/or an elevation in liver function tests that is three times higher than baseline and that cannot be attributed to any other medical or obstetrical condition. These recommendations are for the monitoring of antepartum ZDV toxicity and not for the monitoring of HIV disease in pregnancy.

Newborn Therapy

Physicians caring for newborns who have been exposed to ZDV should be aware of the timing (in utero or newborn) and the duration of the therapy.

The major ZDV-associated toxicity to newborns noted in the ACTG 076 study was a macrocytic anemia. The maximum difference in mean hemoglobin levels between the treatment and control group occurred at three weeks of age, with the lowest absolute hemoglobin reported at six weeks of age. Infants exposed to or treated with ZDV should have biweekly or monthly complete blood counts until these values have stabilized after the discontinuation of newborn therapy. Dose interruption or modification should be considered if anemia is severe and not attributable to other causes.

The long-term effects for intra-uterine ZDV exposure are unknown at present, though long-term follow up of exposed 076 infants is underway. In rodents, high levels of ZDV exposure have resulted in the development of benign vaginal tumors. While this association may well have no relevance for humans, it does suggest the need for continued observation.

Evaluation of infants of HIV-infected mothers should include early testing for HIV infection. HIV antibody of either ELISA or Western blot will be positive regardless of infection status due to transplacental transfer of maternal anti-HIV antibodies from the mother to the fetus. Antibody may persist positive in uninfected children for 6-15 months after birth. Consideration should, therefore, be given to performing either HIV DNA polymerase chain reaction (PCR) analysis or HIV culture. HIV DNA PCR is the preferred method. It should not be done on cord blood because of the risk of contamination by maternal blood. By this method, 38% of infected children will be positive within 48 hours after birth and 93% at 14 days. A negative test at one month may be considered a reliable indication of lack of infection. The State of Michigan provides DNA PCR testing for infants free of charge. For more information, contact 517 335-9453. HIV culture has

similar sensitivity, but is more complex and expensive to perform, and definitive results may require two to four weeks. Assays that detect HIV plasma RNA may also be useful with a positive test considered presumptive of HIV infection. A negative HIV plasma RNA assay should not be used to rule out HIV infection, however.

Currently, it is recommended that DNA PCR retesting be done, at a minimum, at one to two months of age and at four to six months of age; and, antibody testing be done at 18 months of age, because of the theoretical concern that today's more potent antiretroviral regimens in the mother might affect diagnostic sensitivity in the infant. To date, however, there is no evidence that this is so.

Pneumocystic carinii pneumonia (PCP) prophylaxis should be instituted for all infected infants from one month to one year of age, regardless of CD4 level generally with Cotrimoxazole (Bactrim), 5 mg.TMP + 25 mg SMX per kg every day, or twice a day every other day. PCP is rare in the first month of life, and as the sulfa may cause bilirubin problems, prophylaxis is not recommended during the neonatal period. Although PCP can occur at any level of CD4 count, the incidence increases at <150 CD4+ cells/mm^3. If testing for determination of HIV infection is to be delayed for any reason (e.g., inability to get consent, major difficulty in blood drawing, etc.), or if the infant appears at all ill when initially seen, it is better to start prophylaxis presumptively and withdraw it if testing is negative.

Most workers in the field would treat all infected children under 12 months of age with antiretroviral therapy immediately, as soon as a confirmed diagnosis is established, regardless of clinical status, immunologic status, or viral load. Combination therapy with at least two, and preferably, three drugs is strongly recommended. Since the number of available drugs and the information on how they are best used is rapidly changing, the practitioner is advised to consult with and, if possible, refer the infant to a specialist in this area. Treatment study protocols which may be available for such infants may provide substantial reduction in cost of care to third party payors, as well as improve the care to individual infants and the rate at which increasingly beneficial therapies become available. Most treatment study protocols require enrollment prior to administration of antiretroviral therapy, other than the initial six weeks of ZDV.

Program Implementation/Coordination of Health Care Services

RECOMMENDATION: Providers initiating a ZDV regimen in pregnant women for the reduction of mother to child HIV transmission should coordinate services required for the successful completion of ZDV therapy during pregnancy (as per the recommendations presented in this document), during the labor and delivery period, and during the newborn period. Providers of prenatal and maternal or fetal care should develop plans with neonatal or child health care providers to assure ZDV availability for the newborn.

Successful implementation of the recommendations presented in this document will require coordination of the health care services provided by all practitioners who deliver care to women and their newborns. Access to oral ZDV for pregnant women should be assured. Intravenous ZDV should be made available for immediate use in the obstetrical suite. Oral and intravenous ZDV should be readily available in the newborn nursery. Hospitals should develop written plans for coordinating services among labor and delivery, neonatology, and pediatric and pharmacy services to ensure that ZDV is available for patients according to the treatment regimen.

Because the newborn will require six weeks of therapy after delivery, the obstetrical provider should arrange, with the assistance of a pediatrician, to have oral ZDV treatment available at home for the newborn. It is essential that, prior to discharge, the mother be educated in administration of therapy to the newborn. Such planning should enhance compliance with the therapeutic regimen in the immediate postpartum period. Because little is known of the long-term effects of in utero and newborn exposure to ZDV, this therapy should be documented in the infant's medical record.

CONCLUSION

SUMMARY OF CLINICAL GUIDELINES FOR THE ADMINISTRATION OF ZDV FOR THE PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION

1. Identification of Pregnant Women with HIV Infection

   - All obstetricians, midwives, and other obstetrical care providers should routinely discuss the risk of mother to child HIV transmission with their patients.

   - All women's health care providers should routinely offer and recommend HIV antibody testing for all pregnant women and all women considering pregnancy. Testing should be done as early as possible during pregnancy.

2. Documentation of Maternal HIV Antibody Status and/or Maternal HIV Therapies

   - During admission for labor and delivery, routine history taking should include ascertainment of HIV serostatus. For those women who are known to be HIV infected, a history of ZDV use should also be obtained.

3. ZDV Therapy for the Interruption of Mother to Child HIV Transmission in Pregnant Women

   - For women with CD4 cell counts >500 or a viral load <10,000 copies who are greater than 14 weeks gestation, a combined antepartum, intrapartum, and newborn ZDV regimen is recommended per the ACTG 076 study profile.

   - For women with CD4 cell counts <500 and/or a viral load >10,000 copies, combination antiretroviral therapy should be offered in consultation with an experienced HIV/AIDS specialist. Combined antepartum, intrapartum, and newborn ZDV regimen should be discussed and offered. It should be noted that

starting ZDV therapy before pregnancy or during the first trimester solely for the prevention of mother-to-child HIV transmission has not been studied and should not be recommended.

The study randomly assigned women to receive either ZDV or a placebo. The study medication was taken orally during the antepartum period, was given intravenously during labor, and was given to newborns orally for the first six weeks of their life within 24 hours of birth. Dosages suggested for use (modified from the ACTG 076 protocol) were as follows:

During pregnancy: Oral administration of 600 mg of zidovudine (ZDV) in two or three divided doses daily, beginning at 14 weeks of gestation and continued throughout the pregnancy.

During labor and delivery: Intravenous administration of ZDV in a one hour loading dose of 2 mg per kg of body weight followed by a continuous infusion of 1 mg per kg of body weight per hour until delivery.

For newborn: Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg of body weight per dose every six hours) for the first six weeks of life, beginning 8-12 hours after birth.

- For women in labor who have never received any antepartum maternal ZDV therapy (regardless of maternal CD4 cell count), a ZDV regimen combining intrapartum and newborn therapy should be discussed and offered.

- For pregnant women who become intolerant of ZDV following initiation of therapy as per the ACTG 076 trial regime, maternal therapy should be altered. Even if maternal therapy is discontinued, intrapartum and newborn therapy should be discussed and offered unless the maternal intolerance consists of a severe or life-threatening toxicity, such as anaphylaxis.

- For women requiring antiretroviral therapy other than ZDV, including women who have had significant HIV-related disease progression while receiving ZDV, combined intrapartum/newborn ZDV therapy may provide some efficacy in reducing

the risk of perinatal HIV transmission, regardless of the maternal regimen prescribed, and should be discussed and offered.

4. Program Implementation and Coordination of Health Care Services

Providers initiating a ZDV regimen in HIV-infected pregnant women for the reduction of mother child HIV transmission should coordinate services and social support which may be required for the successful completion of ZDV during the antenatal period, the labor and delivery period, and the newborn period. Providers of prenatal and maternal or fetal care should develop plans with neonatal or child health care providers to assure ZDV availability for the newborn.

Medical Reference Contact

HIV/AIDS Treatment Information Services, PHS
1-800-HIV-0440 or http://www.hiv.atis.org

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Improving the odds:

reducing perinatal HIV transmission

SUMMARY OF CLINICAL GUIDELINES FOR THE ADMINISTRATION OF ZIDOVUDINE (ZDV) THERAPY FOR THE PREVENTION OF MOTHER TO CHILD TRANSMISSION

All patients to be tested for HIV antibodies should be provided with pre and post test counseling in compliance with Michigan State HIV Mandatory Counseling and Informed Consent Law (Act 488 of 1988 as amended by Act 200 of 1994, and Act 420 of 1994 - Section 5133). Also note that HIV-positive test results shall be reported to a local health department within seven days on a form provided by the Michigan Department of Community Health (CDC 50.42A or CDC 50.42B) in compliance with HIV Reporting Law (Act 489 of 1988—Section 5114). Contact your local health department for reporting details.

Identification of Pregnant Women with HIV Infection

- All obstetricians, midwives, and other obstetrical care providers should routinely discuss the risk of mother-to-child HIV transmission.
- All women's health care providers should routinely offer and recommend HIV antibody testing for all pregnant women and all women considering pregnancy.

Documentation of Maternal HIV Antibody Status or Maternal HIV Therapies

- During admission for labor and delivery, routine history taking should include ascertainment of HIV serostatus. A history of ZDV use should also be obtained for those women known to be HIV infected.
- The Prenatal Care Requirement Law (Act 491 of 1988, as amended by Act 200 of 1994— Section 5123) requires that pregnant women be tested for HIV, hepatitis B, and venereal disease at the initial examination, unless tests are medically inadvisable or the woman does not consent to testing. It also requires documentation of the test results in the record.

ZDV Therapy for the Interruption of Mother-to-Child HIV Transmission in Pregnant Women
For women with CD4 cell counts >500 or a viral load <10,000 copies who are greater than 14 weeks' gestation, a combined antepartum, intrapartum, and newborn ZDV regimen is recommended as per the ACTG 076 study profile.
For women with CD4 cell counts <500 or a viral load >10,000 copies, the use of combination antiretroviral therapy with combined antepartum, intrapartum, and newborn ZDV regimen should be discussed and offered. It should be noted that starting ZDV therapy before pregnancy or during the first trimester solely for the prevention of mother-to-child HIV transmission has not been studied and should not be recommended.
For women in labor who have never received any antepartum maternal ZDV therapy (regardless of maternal CD4 cell count), a ZDV regimen combining intrapartum and newborn therapy should be discussed and offered.

Recommended ZDV Dosages to Reduce the Risk of Mother to Child HIV Transmission

- Maternal therapy: second and third trimester: 200 mg PO, 3 doses/day. Therapy should start as early in the second trimester as possible.
- Intrapartum: Intravenous ZDV during delivery; 2 mg/kg loading dose over 1/2 to 1 hour followed by continuous infusion of 1 mg/kg per hour until the cord is clamped.[1,2,3,4]
- For patients undergoing induction of labor, intravenous therapy should begin at the time induction of labor begins. For an elective cesarean section, intravenous therapy should begin 4 hours before the time of surgery.
- Newborn: ZDV syrup, 2 mg/kg per dose, PO, 4 doses/day for 6 weeks; therapy should start within 8 to 12 hours of birth.[5]

  If the infant remains NPO and cannot begin oral ZDV within 8 to 12 hours of life, intravenous ZDV (1.5 mg/kg every 6 hours) can be given.

  At present, there is insufficient pharmacokinetics information to recommend dose modifications for premature infants.

[1] If delivery is anticipated in less than 1/2 hour from the time of arrival, a bolus infusion of ZDV can be given. The drug must be diluted prior to administration, the maximum concentration that can be given is 4 mg/ml.

[2] ZDV is compatible in the following IV fluids. Normal Saline, D5 Normal Saline, Lactated Ringers, and D5 actated Ringers.

[3] The infusion can be piggybacked into the main IV line. At present, information regarding compatibility with other commonly used obstetrical medications is unavailable.

[4] Pharmacokinetics data on oral dosing during pregnancy are not currently available. A continuous IV infusion should result in maximal fetal/newborn drug levels. If IV ZDV is not available, an oral loading dose of 400 mg followed by 200 mg every 2 hours may be considered. This is based on historical pharmacokinetics information. The efficacy of this regimen has not been studied.

[5] If no intrapartum therapy has been given, newborn therapy should start as soon after birth as possible. It is unlikely that any benefit will be gained if therapy is started after 48 hours.

For Medical Reference Contact

HIV/AIDS Treatment Information Services, PHS .1-800-HIV-0440 or http://www.hiv.atis.org

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